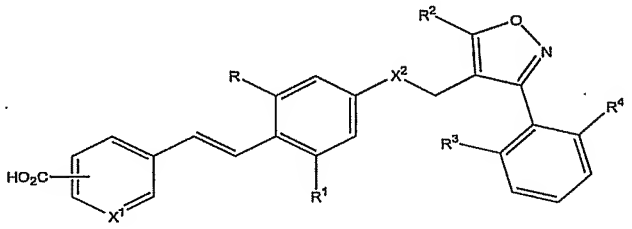
REMARKS

Currently, claims 4, 6, 8, 10 and 12-14 are pending in the application. This includes independent claim 4 which has been amended by incorporating the limitations of claim 5. Claims 13 and 14 are new and supported throughout the specification including but not limited to paragraph [0067]. Claims 1-3, 5, 7 and 11 have been canceled.

Independent claim 4 claims a method of reducing development of liver fibrosis in a mammalian subject with histopathological fibrotic changes or changes in disease markers consistent with fibrotic disease comprising administering to the mammalian subject a Farnesoid X Receptor agonist in an amount effective to reduce or slow the rate of fibrotic changes associated with liver fibrosis wherein the Farnesoid X Receptor agonist comprises a compound of Formula (I):



wherein X^1 is CH or N; X^2 is O or NH; R and R^1 are independently H, lower alkyl, halogen, or CF_3; R^2 is lower alkyl; R^3 and R^4 are independently H, lower alkyl, halogen, CF_3, OH, O-alkyl, or O-polyhaloalkyl.

Claims 4, 6, 8, 10 and 12 stand rejected pursuant to 35 U.S.C. § 112, second paragraph, as being indefinite for reciting the administration of a "therapeutically effective amount" of an FXR agonist because the "preamble of the claim is not linked to the body of the claim in such a way as to clearly convey which condition/disease the therapeutically effective amount is administered for." (06/11/2009 Office Action, p. 3.) While Applicant respectfully disagrees, in the interest of advancing prosecution, Claim 4 as currently amended claims, *inter alia,* that it is directed to reducing the development of liver fibrosis by administering a therapeutically effective amount of a Farnesoid X Receptor agonist as a therapeutic treatment to reduce or slow the rate of fibrotic changes associated with liver fibrosis. Respectfully, the rejection of claim 4 pursuant to 35 U.S.C. § 112, second paragraph, should be withdrawn and the claims allowed.

Claims 4, 8, 10 and 12 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement for failing to provide "structural

characteristics or chemical formulas aside from the express identification of FXR agonist per se that would provide adequate written description of the genus of compound capable of behaving as an FXR agonist that Applicant was actually in possession of, and intended to be used within the context of the present invention." (06/11/09 Office Action, p. 4.) While Applicant respectfully disagrees, claim 4 has been amended to further prosecution and renders this rejection moot.

Claims 4, 6, 8 and 10 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Office Action states "[t]he specification provides no direction or guidance for determining the particular administration regimens (e.g., dosages, timing, administration routes, etc.) necessary to ***prevent*** hepatic fibrosis." (06/11/09 Office Action, p. 8.) While Applicant respectfully disagrees with this position, in the interest of promoting and forwarding prosecution, independent claim 4 has been amended to remove all reference to the term "preventing."

Claims 4, 6, 8 and 10 also stand rejected under 35 U.S.C. § 102(e) as being anticipated by Kliewer et al. U.S. Patent Publication No. 2003/0203939 ("Kliewer '939") as well as anticipated by Jones et al. U.S. Patent Publication No. 2005/0107475 ("Jones '475")[1]. However, neither Kliewer '939 nor Jones '475 anticipate Applicant's independent claim 4.

Kliewer '939 discloses methods for the treatment of cholestatic liver disease and reduction and prevention of hepatic injury resulting from cholestasis via administration of a FXR ligand. (Abstract.) Kliewer '939 explains:

> [0002] **Cholestasis is defined as *the impairment or cessation of bile flow*** and occurs in a variety of human liver diseases. Although there are various pathogenic causes of cholestasis, hepatocellular injury and associated liver dysfunction commonly result (Trauner et al. N. Engl. J. Med. 1998 339:1217-27).
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> [0004] Using a potent selective FXR ligand, it has now been found that FXR ligands are hepatoprotective in bile duct-ligated (BDL) rats, a well-characterized model of extrahepatic cholestasis. These data are indicative of **FXR ligands being effective in the treatment of cholestatic liver disease**.
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> [0009] **Ligand binding of the FXR nuclear receptor can result in the alteration of expression of various genes that FXR aids in**

[1] Applicant does not acquiesce to the status of Kliewer '939 or Jones '475 being available as "prior art" under any applicable section of *35 U.S.C. § 102* and hereby expressly preserves all positions relating to this issue.

> **regulating, including genes involved in lipid absorption and digestion in the small intestine and lipid homeostasis in the liver.** Examples of such genes include, but are not limited to, genes involved in bile acid transport, lipid absorption, cholesterol biosynthesis, proteolysis, amino acid metabolism, glucose biosynthesis, protein translation, electron transport, and hepatic fatty acid metabolism. FXR often functions as a heterodimer with the Retinoid X Receptor (the FXR/RXR heterodimer). The inventive method herein includes using this technology to affect bile acid and cholesterol homeostasis such that, ultimately, liver injury from cholestatic liver diseases is prevented or reduced and in treating cholestatic liver diseases in a mammal, including man. Thus **the present invention provides methods for treating cholestatic liver diseases in a patient in need thereof via administration of an FXR ligand.**
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> [0010] **By "cholestatic liver disease" it is meant to be inclusive of any condition that impairs bile flow and results in impairment of liver function**. Examples of such conditions include, but are not limited to cholestatic liver diseases, such as primary biliary cirrhosis, primary sclerosing cholangitis, cystic fibrosis, and intrahepatic cholestasis of pregnancy.

Simply put, Kliewer '939 discloses a method of administering FXR ligands to remedy impairment or cessation of bile flow. However, Kliewer '939 is completely silent with respect to effects on liver fibrosis as well as reducing or slowing the rate of fibrotic changes associated with liver fibrosis. Thus, Kliewer '939 does not anticipate Applicant's claimed method of administering FXR.

Jones '475 discloses treatment of human hepatocytes with FXR agonists to alter cell metabolism such as for use as a pharmaceutical weight loss method. (Abstract.) Jones '475 explains:

> [0005] A first aspect of the present invention is a method of **increasing leptin release from the adipocyte cells of a mammalian subject, by administering an FXR agonist** to the subject. Leptin release is increased, compared to the leptin release that would occur without FXR agonist administration.
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> [0006] A further aspect of the present invention is a method of **decreasing glucose uptake by the adipocyte cells of a mammalian subject, by administering an FXR agonist** to the subject. Glucose uptake is decreased compared to that which would occur in the absence of FXR agonist administration.
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> [0007] A further aspect of the present invention is **a method of treating a mammalian subject to achieve weight loss, by administration of a pharmaceutically acceptable FXR agonist**. The

> subject's weight is decreased, compared to that which would occur in the absence of FXR agonist treatment.
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> [0012] **The present invention relates to the use of Farnesoid X Receptor (FXR) agonists to affect the metabolism of cells, and as a pharmaceutical treatment for weight control and weight loss.** The present inventors determined that activation of the nuclear receptor FXR by a bile acid agonist, as well as by a small molecule FXR agonist, caused an increase in transcription of a human Fibroblast Growth Factor gene (hFGF19), leading to an increase in the quantity of mRNA encoding the fibroblast growth factor. Accordingly, **in humans expression of FGF19 and its downstream activity can be modulated using FXR agonists.** Human FGF19 has been reported to induce leptin release from rat adipocyte cells and decrease glucose uptake by rat adipocyte cells; transgenic mice expressing hFGF19 have been reported to be less fat than their nontransgenic littermates; increased oxygen consumption has been reported in mice administered recombinant FGF-19; and administration of FGF-19 has been suggested as a treatment for obesity (WO 01/18210, Genentech).

As Jones '475 explains, it discloses a method of using FXR to alter the metabolism of adipocyte cells in order to increase the amount of leptin they release and reduce the amount of glucose they uptake. This results in being able to reduce the body mass of a mammalian subject to which the FXR is administered. Plainly, this use of FXR does not anticipate Applicant's independent claim 4 which is directed to reducing or slowing the rate of fibrotic changes associated with liver fibrosis. Accordingly, neither Kliewer '939 nor Jones '475 anticipate Applicant's independent claim 4. Thus, the rejection of claim 4 pursuant to 35 U.S.C. § 102 should be withdrawn and the claims allowed.

Applicants believe the present claims are in condition for allowance and such action is respectfully requested. If the Examiner has any outstanding issues with the pending claims, he is encouraged to telephone the undersigned at (919) 483-8406 for expeditious handling.

Respectfully submitted,

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